IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:	**Group Art Unit:** 1644
YAJUN GUO	**Examiner:** T. Cunningham
Serial No.: 08/872,527	
Filed: June 11, 1997	
For: CELLULAR VACCINES AND IMMUNOTHERAPEUTICS AND METHODS FOR THEIR PREPARATION	

RESPONSE TO OFFICE ACTION

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

The Examiner is thanked for the courtesy extended during the telephonic interview of January 20, 1999. In response to the Office Action mailed July 14, 1999, please consider the following remarks.

Pending claims 1-22 and 33-65 are directed to immunogenic compositions and methods that make use of stimulated, autologous, diseased target cells that have been armed with at least one attached bridge molecule that functions to facilitate and enhance T cell recognition and response.

CERTIFICATE OF MAILING
(37 C.F.R. §1.8a)

I hereby certify that this paper (along with any referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as First Class Mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Jeanette M. Olivera
Name of Person Mailing Paper

October 13, 1999
Date of Deposit

Jeanette M. Olivera
Signature of Person Mailing Paper

The Examiner has rejected the claims on various grounds. Claims 1-22 and 33-65 are rejected under 35 UCS 112 as allegedly indefinite and nonenabling. The claims are also rejected under 35 USC 103 as allegedly obvious over a combination of references. Last, the Examiner requests verification as to which of the pending claims read on the elected species of bridge molecule, bispecific CD28:gp55 monoclonal antibody. The Applicant responds to each of the rejections and the request as follows.

I. Definiteness under 35 USC 112, ¶2

The Examiner alleges that there is ambiguity in the scope of the claim term, "bridge molecule," and requests specific clarification as to whether the term is intended to include natural bridges, like B7, that possess a transmembrane domain. Although the bridge molecules of the present claims may functionally interact with such "natural" bridges on diseased cells, and may even include various component domains thereof, e.g., extracellular ligand or receptor domains, the claimed molecules do not embrace such natural bridges in their entire or natural state. Thus, the "bridge molecules" of the present claims do not possess functional transmembrane domains.

The Applicant respectfully submits that the rejection is mooted by this clarification, and accordingly should be withdrawn.

II. Enablement under 35 USC 112, ¶1

A. No deposit is necessary

The Examiner alleges two separate grounds for why the claimed invention is not enabling. First, the Examiner requires that bispecific antibodies comprising gp55 determinants as claimed either be deposited or else demonstrated to be obtainable by a repeatable method set forth in the specification. The Applicant contends that page 32, lines 13 et seq. of the application sufficiently

demonstrate the latter. That passage describes in detail how to generate and isolate antibodies of desired specificity. Moreover, the Examiner's position is inconsistent with his later position on page 6, paragraph 3, second sentence, wherein he states, "The exact identity of the antibody that binds to the target cell (for the elected species gp55) *does not appear to be critical* to the invention, see e.g. page 10, lines 25-27 of the specification." (emphasis added).

This statement correctly illustrates the point. The exact antibody identity (specificity and affinity) is not critical, and suitable antibodies may readily and reproducibly be generated from the guidance provided in the specification. Thus, it is not be necessary to supply the exact antibodies used in the specification. One of ordinary skill can reproducibly obtain suitable antibodies without engaging in undue experimentation. See 37 CFR 1.802 (b) and MPEP § 2404.

The Applicant therefore respectfully requests that this ground of rejection be withdrawn.

B. The specification is enabling for the treatment of both immunogenic and nonimmunogenic tumors

The Examiner next alleges, "the specification, while being enabling for treatment of immunogenic tumors..., does not reasonably provide enablement for treatment of nonimmunogenic tumors. This is incorrect.

The specification clearly teaches at page 29 bridging page 30, lines 30-03, that HEPA 1-6 *is* nonimmunogenic: "Hepa 1-6 cells lack both MHC class I and B7 molecules on their cell surfaces *and do not induce a host immune response* even when transfected with genes encoding the B7-1 or B7-2 molecule." (emphasis added). Furthermore, Example 6.6 on page 37 of the specification teaches that nonimmunogenic Hepa 1-6 cells can be treated to be immunogenic, and then introduced in vivo to cure established hepatomas consisting of wild-type Hepa 1-6 cells.

As demonstrated, the specification therefore *is* enabling for non-immunogenic tumor cells, and the Applicant respectfully requests that the rejection be withdrawn.

III. Unobviousness under 35 USC § 103

The Examiner has alleged the claims to be obvious over the references Wang or Vanky in view of Renner or Bohlen, Darlington, Chapoval and Krummel.

A. What the references teach

Wang et al teach cytokine-induced elevation of MHC I complexes in autologous, *mixed* lymphocyte-tumor cell cultures (MLTCs), and consequential functional association with T cells as measured in vitro using cytotoxicity assays. The Applicant emphasizes that the cells used in Wang, contrary to the instant invention, were mixed and not pure. This has important consequences for patentability as will be demonstrated shortly.

Vanky et al., like Wang, also teach MLTC response to cytokines and consequent functional association with T cells in vitro. The emphasis is on cell lysis.

The Examiner correctly notes that neither Wang nor Vanky teaches or motivates the additional use of bispecific monoclonal antibody (Bi-Mab) bridge molecules. Office Action, pg. 6, ¶2. Rather, the focus of these references is concerned merely with determining the mechanistic function of stimulated tumor cells and T cells upon cytokine administration.

Renner described the administration of free, soluble Bi-Mabs (CD30:CD28 and CD30:CD3) to "SCID" mice that bore established human tumors followed by mixed lymphocytes (effector cells included) that had been pre-stimulated with Bi-Mabs. As will be discussed further below, this is very different and inferior to what the Applicant claims. (See Declaration of Dr. Yajun Guo, Attached hereto as **Exhibit 1**). As clearly noted in Renner, SCID mice have no functional T cells.

Renner had to add functional T cells back to the system. Thus, the universal set of functional T cells used in Renner was already armed with BiMabs. A further difference with Renner's system is that "...only the combination of *both* BiMabs [was] able to induce sufficient tumoricidal activity to cure the tumors." p. 834, third column, top. These differences are significant.

For example, Dr. Guo's Declaration makes clear that tumor clearance using Renner's method would not have been effective in an in vivo system already bearing a natural supply of functional, unarmed T cells, but that the claimed invention, by contrast, clearly *is* effective under such conditions and surprisingly so. Moreover, Dr. Guo's method and combination is completely effective using but one type of BiMab (although others may effectively be used, alone or in combination).

Bohlen also described Bi-Mab strategies to bridge tumor cells and T cells, but not in the unobvious way that the Applicant does. Bohlen specifically taught that BiMabs with both tumor-specific antigen affinity and CD3 or CD28 affinity could stimulate T cells to proliferate *in vitro*. Bohlen suggests in the last sentence of his abstract that these in vitro results can be extrapolated to in vivo systems by simply adding the BiMabs to tumor afflicted patients. Once again, and as further demonstrated below and in Dr. Guo's Declaration, doing so is vastly ineffective compared with the results achieved using the claimed invention.

Chapoval, like Bohlen and Renner, also teaches BiMabs as functional bridges between T cells and tumor cells but suffers the same deficiency. Chapoval combined all the components of the system in vitro--T cells, tumor cells, and BiMabs. Chapoval also taught adding BiMabs straight into the in vivo recipient and monitoring effect. Although success was demonstrated by way of resultant T cell proliferation and cytotoxicity, the magnitude of that success is inferior the success achieved using the Applicant's claimed combination and method. Furthermore, Chapoval's administration of

unadulterated insoluble BiMab was demonstrated to be *toxic* in vivo unless a specific form of Fab was used. (p. 1302, second column, second paragraph). The Applicant's insoluble BiMab system that is preconjugated to tumor cells, by contrast, avoids this negative response. This is discussed in greater detail below.

Krummel et al. describe the opposing effects of T cell CD28 and CTLA-4 surface molecules when contacted by APC B7 surface molecules. Contact of CD28 stimulates T cells, whereas contact of CTLA-4 inhibits them. The Applicant's methods and combinations exploit this by promoting CD28 binding over CTLA-4, but do so in the unobvious way described below.

B. How the claimed invention is unobviously different from the references cited

1. Pre-attachment of BiMabs to tumor cells ex vivo, *outside* the presence of T cells, results in surprising results

The cited art teaches that BiMabs can be used to facilitate the functional interaction of T cells and tumor cells. Other art teaches that cytokine treatment can be helpful. Assuming there is a proper motivation to combine these references, the combined references still do not teach what the invention teaches.

The claimed invention takes an inventive step forward in establishing that the *order* and *manner* in which components are combined is very important, and until now, unappreciated. This order and manner are explicit in the claims and in no way addressed in the cited art, which merely teaches a random, uncontrolled addition of components, with corresponding poor results. The claimed invention, by contrast, is directed to a *pre-attachment* of BiMabs to tumor cells, followed by adminstration, preferably after elimination of substantially all unreacted BiMab, to an afflicted patient. The reaction also preferably takes place in the *absence* of T cells.

These differences, alone or together, result in a marked increase in immunogenicity upon administration to a patient. The Applicant believes that this is due to the double-priming of tumor cells, first through stimulation of tumor antigen production using, e.g., cytokines, and second through the specific conjugation of those same tumor cells with BiMab. This is important because

upon administration to a patient these armed tumor cells are primed to react quickly and optimally with naïve T cells.

If as Wang and Vanky teach, *mixed* lymphocyte-tumor cell cultures (MLTCs) are used, no or suboptimal results are achieved because co-culturing ex vivo results not only in T cell stimulation, and proliferation, but also in premature cytotoxicity, and hence *killing* of tumor cells *in vitro* before they can be of any use in vivo. Obviously, if they are first eliminated through killing or masking, they cannot be effective later. This illustrates that a key feature of the Applicant's invention is to delay cytotoxicity until *after* adminstration to the patient. The claimed vaccine is unique in that it then acts like a systemic magnet (hence the claimed immunogencity) for naïve T cells that then attach to the vaccine cells (via the unreacted end of the BiMab molecules), proliferate, and then re-attach with cytotoxic effect, not only to the vaccine cells, but also to unstimulated, unattached tumor cells already established in the patient. The Applicant's method is hence extremely effective at clearance of established tumors relative to what was taught in the art. The claimed invention recognizes a heretofor unappreciated problem and very effectively solves it.

Furthermore, if unattached BiMab is added to MLTCs cultures, or directly into a patient (as suggested by Renner, Chapoval, and Krummel), any effect is attenuated at best because a significant portion of BiMab can be expected to bind T cells, but not tumor cells, and vice versa. This results in undesirable site occlusion that is explained in Dr. Guo's accompanying Declaration. The diagrams illustrate how BiMab-bound tumor cells cannot thereafter bind a T cell that, itself, is already bound to another, unattached BiMab molecule. It is therefore important to first react BiMab only or primarily with pre-stimulated tumor cells, preferably outside the presence of T cells. To do otherwise, as demonstrated, defeats the invention purpose. The art thus can be said to teach away from what the claims teach.

More support for the Applicant's position may be found in the accompanying Declaration of Dr. Guo, which demonstrates very real and surprising results when using his claimed invention over what was known in the art.

For the foregoing reasons, it is respectfully requested that the rejection for obviousness be withdrawn.

IV. Identification and verification of claims that read on the elected species

The Examiner has requested that the pending claims be examined for concordance with the elected species. The Examiner has suggested that claims 5, 11, 14-15, 16-17, 18-19, 39-41, 42-48, 55-56, 58-62, and 64-65 are all drawn to the nonelected species and will therefore be withdrawn from consideration. The undersigned respectfully disagrees with this characterization in light of MPEP § 806.04(f), which states that claims to be restricted to different species must *recite mutually exclusive characteristics*.

To illustrate, the following hypothetical is invoked. An independent claim is drawn to a widget. A dependent claim thereof is drawn to a blue widget, and yet another dependent claim is drawn to a red widget. Because a widget in the abstract cannot at once be both pure red and pure blue, these claims are said to be mutually exclusive of one another, and hence to constitute different species.

In the instant claims, no such species relationship can be attributed to claims 5, 11, 14-15, 16-17, 18-19, 39-41, 42-48, 55-56, 58-62, and 64-65, as the Examiner suggests. Hence it is respectfully submitted that these claims all be properly considered together, and not separately.

V. Conclusion

For the foregoing reasons, it is respectfully submitted that the pending rejections are overcome, should be withdrawn, and that the claims are in full condition for allowance.

No fee is believed due in connection with this response. However, if wrong for any reason, the Examiner is authorized to debit Deposit Account No. 12-2475 for the appropriate amount.

Respectfully submitted,

LYON & LYON LLP

Dated: September 20, 1999

By: _____
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